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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HIROSHI MIURA, ET AL.	: EXAMINER: PALENIK, JEFFREY T.
SERIAL NO: 10/551,901	:
FILED: OCTOBER 4, 2005	: GROUP ART UNIT: 1615
FOR: COMPOSITION CONTAINING MEDICINE EXTREMELY SLIGHTLY SOLUBLE IN WATER AND METHOD FOR PREPARATION THEREOF	:

DECLARATION UNDER 37 C.F.R. §1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Toshio INAGI, hereby declare:

1. I am a named inventor in the above-captioned patent application.

2. I am a graduate of the University of Tokyo. I received a PhD in the field of Pharmaceutical Sciences in 1983.

3. I have been employed by Kowa Co., Ltd. ("Kowa"), the assignee of the above-captioned patent application, for 37 years. I have been employed at Kowa as a director of preparation and research relating to mechanisms of percutaneous absorption.

4. I am familiar with and have worked with the products and methods described in the above-captioned patent application.

5. I am familiar with U.S. Patent Application Publication No. US 2002/0047058 to Verhoff et al. ("Verhoff") and U.S. Patent No. 5,538,728 to Yanaki et al. ("Yanaki"), which I understand have been cited against the above-captioned patent application.

6. I and/or those under my direct supervision and control carried out the following experimentation.

Example 1

30 mg of a very low water-soluble drug, 300 mg of a porous silica material having an average pore diameter of 1000 nm and a specific surface area of 67 m^2/g, and 120 g of dry ice were placed in a Portable Reactor (product of Taiatsu Techno Corporation). The reactor was heated to 50 °C, to increase the pressure in the reactor to 18 MPa. The temperature and pressure in the reactor were then maintained for five hours while stirring. Heating of the reactor was ceased, the reactor was allowed to cool to room temperature and carbon dioxide was discharged from the reactor. The resulting product was very low water-soluble drug-containing composition.

Example 2

30 mg of the very low water-soluble drug employed in Example 1, 300 mg of a non-porous silica material having a specific surface area of 40 m^2/g, and 120 g of dry ice were placed in a Portable Reactor (product of Taiatsu Techno Corporation). The reactor was heated to 50 °C, to increase the pressure in the reactor to 18 MPa. The temperature and pressure in the reactor were then maintained for five hours while stirring. Heating of the reactor was ceased, the reactor was allowed to cool to room temperature and carbon dioxide was discharged from the reactor. The resulting product was very low water-soluble drug-containing composition.

Dissolution Test

Each of the very low water-soluble drug-containing composition of Example 1 and the very low water-soluble drug-containing composition of Example 2 were subjected to a dissolution test. The dissolution test was carried out by the paddle method, which is a general test method specified by Japanese Pharmacopoeia. Specifically, 5 mg of the very low water-soluble drug-containing composition of Example 1 were fed into 900 mL of a test solution of 0.3% aqueous sodium lauryl sulfate. The mixture was subjected to the dissolution test at temperature of 37 ± 1 °C with paddle revolutions at 50 rpm.

After mixing for 5 minutes, 30 minutes, 60 minutes and 120 minutes, the amount of the very low water-soluble drug dissolved in the test solution was determined using a liquid chromatograph employing a reversed-phase column (Inertsil ODS-2, product of GL Sciences Inc.), which yielded the percent dissolution (%) of the very low water-soluble drug. The procedure was repeated with the very low water-soluble drug-containing composition of Example 2.

The results are shown in the TABLE below.

TABLE

			Example 1	Example 2
Very low water-soluble drug (mg)			30	30
Porous silica material (mg)			300	-
Non-porous silica material (mg)			-	300
Dry ice (g)			120	120
Average pore diameter (nm)			1000	-
Specific surface area (m^2/g)			67	40
Percent dissolution (%)	Stirring time (min)	5	0.2	5.0
		30	0.7	5.4
		60	1.0	7.0
		120	1.4	8.6

7. I understand that, e.g., claim 1 of the above-captioned patent application, requires that a very low water-soluble drug and a porous material having a particular average pore diameter and a particular specific surface area be subjected to treatment with a supercritical or subcritical carbon dioxide fluid. As is evident from the results shown in the TABLE above, subjecting a very low water-soluble drug and either a non-porous material or a porous material not having the particular average pore diameter and specific surface area of claim 1 to treatment with a supercritical or subcritical carbon dioxide fluid, does not result in improved solubility of the very low water-soluble drug in comparison with the improved solubility of the compositions of claim 1 as shown, e.g., in Table 1 of the above-captioned patent application. The improved performance exhibited by compositions according to claim 1 of the above-captioned patent application, relative to compositions disclosed or suggested by Verhoff and Yanaki, is significant and unexpected.

8. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true; these statements were made with the knowledge that willful false statements are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing therefrom.

Date: June 17, 2009

Toshio INAGI